Focus

Are Pesticides a Problem?

U.S. federal law under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) defines a pesticide as "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any insects, rodents, nematodes, fungi, or weeds, or any other form of life declared to be pests, and any substance or mixture of substances intended for use as a plant regulator, defoliant, or dessicant." Such a definition easily leads to the correct perception that a staggering number of pesticide products are present in our environment. Indeed, more than 34,000 pesticides derived from about 600 basic ingredients are currently registered for use in this country by the U.S. Environmental Protection Agency, of which agriculture uses over 20,000. The use of agricultural pesticides in the United States occurs on more than 900,000 farms, where approximately 75% of all cropland and 70% of all livestock are treated with these substances. Although great benefits have been derived from the use of pesticides, not the least of which is the ability to produce large amounts of food crops on small acreages at a savings of millions of dollars a year, scientists are continuing to realize the potential dangers of these substances, and the public will be forced to weigh these benefits against the costs to human health.

In the United States, agriculture accounts for over two-thirds of expenditures on pesticides and three-fourths of the total 1.1 billion pounds of pesticide active ingredients used annually in recent years. These chemicals are targeted at a vast array of pests. There are 410 weed species, 34 mite species, 137 plant diseases, 22 nematode species, and 304 insect species that are injurious to crops in the United States. Of roughly 817 million pounds of pesticides used by U.S. agriculture in 1991, 495 million pounds were herbicides to control weeds, 175 million pounds were insecticides, and 75 million pounds were fungicides for disease control. "Other" pesticides (rodenticides, fumigants, and molluscicides) accounted for 72 million pounds. Although agricultural pesticide usage has been relatively stable in recent years, it continues to be spread out in vastly different growing regions nationwide, creating thousands of pest, pesticide, crop, and region combinations.

Double-edged Plowshare

References to the use of pesticides can be found as far back as Homer's mention of the fumigant value of burning sulfur. However, concerns about a dual character to most pesticides—that they control pests but at the same time pose potential toxicity to nontarget species including humans, or are otherwise environmentally detrimental—did not become widespread until the late 1960s. Then problematic issues surrounding chlorinated hydrocarbons emerged, the potential of pesticides for bioaccumulation and long-term toxicity became widely recognized, and pest resistance became increasingly evident. Farmers stopped using DDT and other chlorinated compounds in favor of organophospates and carbamates, which although more acutely toxic, do not persist in the environment. Meanwhile, government came under tremendous public pressure to put an end to the use of DDT and chlorinated pesticides. This call arrived amid a growing public demand for cleaner water, air, and land and contributed directly to the establishment of the Environmental Protection Agency in 1970. From the Food and Drug Administration, EPA inherited the responsibility to set tolerances, or legal residue limits, for pesticides in food. From the Department of Agriculture, EPA gained authority to register pesticides and regulate their use. In 1972, EPA revoked the use of DDT on all food sources in the United States. The World Health Organization, however, still reserves the right to use DDT on particularly virulent outbreaks of malaria because no other pesticide is as effective against nonresistant mosquitoes.

Beginning in the 1960s and continuing through the 1970s and 1980s, the United States saw the introduction of a new generation of pesticides, based largely on a more thorough understanding of biological and biochemical mechanisms, and which are often more effective at lower doses than older pesticides. Examples of these new pesticides include the organophosphates, originally derived from nerve gas, and carbamates. Humans are considerably less sensitive to some of these pesticides than are insects due to a greater ability to degrade these chemicals enzymatically. Other new-generation pesticides also include the herbicidal sulfonylureas and the synthetic fungicides metalaxyl and triadimefron and pesticides such as the synthetic, light-stable pyrethroids, derivatives of botanical pyrethrins, which can be applied in gram quantities rather than pounds per acre.

The emergence of pest management programs, a result of improved knowledge in host–pest interactions, has helped decrease insecticide use on major crop commodities such as corn, soybeans, cotton, and wheat since the 1960s. Today, there is great interest in genetically engineered microbial agents, including development of pest-resistant transgenic crops and other biological pest control methods.

Robert Menzer, director of EPA's Environmental Research Laboratory in

The Persistence of Pesticides

Ancient times: Ashes, common salts, and bittern are used as herbicides

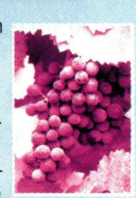
1st century AD: Roman naturalist Pliny the Elder, in his *Historia naturalis*, advocates the use of arsenic as an insecticide; suggests soda and olive oil for treatment of legumes

16th century: Chinese farmers use arsenicals and nicotine in the form of tobacco extracts as insecticides

1850s: Pyrethrum and soap see wide use in the West as insecticides; a wash of tobacco, sulfur, and lime used to combat insects and fungi

1867: The pigment Paris green, an impure form of copper arsenite, is introduced into United States to control outbreaks of Colorado potato beetle; within a decade Paris green and kerosene oil emulsion are used against a wide variety of chewing and sucking insects

1896: A French grape grower applies Bordeaux mixture, a formula-tion of copper sulfate and calcium hydroxide, observes nearby weeds turning black, and the idea of selective chemical herbicides is born



1900: Sulfuric acid, copper nitrate, and ammonium and potassium salts are used as selective herbicides

1900–1950: Sodium arsenite solutions become the standard herbicides and are used in large quantities

1913: Organomercury seed dressings introduced in Germany

1913–1939: First of several dithiocarbamate fungicides patented in the United States

Gulf Breeze, Florida, sees a need to keep a historical perspective when considering pesticide development and use. He emphasizes that without this perspective one can draw wrong conclusions, such as the belief that most things natural are good, while most things synthetic are bad, or at least potentially evil. "You have to look at the priorities of the times. Beginning just after World War II, increasing crop yield to feed a rapidly growing population was considered paramount. And so, DDT and other synthetic chemicals were embraced as ideal and safe for the job. And mankind benefited tremendously from DDT's use in controlling malaria and yellow fever. As priorities shifted to concerns about toxicity, we've moved toward more unstable, very selective, and more expensive chemicals such as pyrethroid compounds, which in the future will be increasingly integrated with other methods of control," said Menzer.

Who Is at Risk?

A reader of Rachel Carson's *Silent Spring* would find it hard not to be moved by its evocative introduction, in which she foretold of a town in the heart of America where all life seemed to live in harmony with its agricultural surroundings:

> Then a strange blight crept over the area and everything began to change. . . . Everywhere was the shadow of death. The farmers spoke of much illness among their families. In the town the doctors had become more and more puzzled by new kinds of sickness appearing among their patients. There had been several sudden and unexplained deaths, not only among adults but even among children, who would be stricken suddenly while at play within a few hours. . . .

Carson's "blight" was synthetic chemical pesticides, including DDT. And encompassed within her bleak vision of 30 years ago are controversial issues that today surround the potential for adverse health effects from pesticide exposure and use: What is the potential for, and the evidence of, acute and chronic adverse effects? Who is most susceptible? Is there cause for concern about residues in food sources, no matter how infintessimal?

In the United States, 2.1 million farmers, 6 million farm family members, and nearly 3 million hired farm workers make up a large portion of people having potential contact with agricultural pesticides. In addition, people employed in the manufacture and formulation of agrichemicals, as well as other plant growers and harvesters, and the more than 1 million aerial applicators, fumigators, professional ground and structural applicators and loaders, also are likely to have significant exposure to pesticides.

A major source of nonoccupational pesticide exposure in the general population results from pesticide use in and around the home. EPA estimates that 69 million American households, or more than 85% of the nation's total families, store and use pesticides.

Acute Health Effects

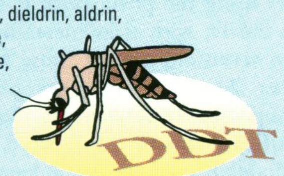
The absence of a national database prevents the compilation of accurate or complete statistics regarding incidence of death and injury from acute pesticide poisoning in the United States. Based on extrapolation of hospital surveys, an estimated 20,000 people receive emergency care annually for actual or suspected pesticide poisoning, and approximately 10% are admitted to the hospital. Each year, 20–40 people die of acute pesticide poisoning in the United States. In California, where acute pesticide poisoning is required to be reported to state health authorities, 1987 case surveys listed about 17,000 exposure incidents, of which 30–60% were symptomatic. Of these, approximately 1,500 were occupational, with systemic toxicity demonstrated symptomatically in 744.

Still unknown, however, is the number of affected workers in the United States who never see a doctor and who therefore go undiagnosed and unreported. "More effective reporting systems are needed before the magnitude of adverse health conditions from acute exposures can be well monitored," says Aaron Blair, chief of NCI's Occupational Studies Section. Blair's point is echoed by the World Health Organization, which considers acute pesticide poisoning a major health problem globally. WHO estimates that between 1 and 5 million cases of acute pesticide poisoning occur annually, largely in underdeveloped nations where pesticide education, monitoring, and safety equipment is either limited or unavailable and where use of extremely toxic agrichemicals is more extensive. Yet even if morbidity and mortality figures remain incomplete, effects of acute exposure to pesticides are well established.

Neurotoxicity. In the United States, most episodes of acute occupational poisoning are due to organophosphate and carbamate insecticide exposure. Poisoning is manifest as neurotoxicity, as the primary toxic effect of both compounds is cholinesterase inhibition in the blood and nervous system. This action, which prevents degradation of acetylcholine at the neuronal synapse, results in overactivity of cholinergic neurons. Significant reductions in plasma cholinesterase are associated with a number of acute and subacute neurotoxic effects: muscle tremors, twitching and weakness, anorexia, nausea, vomiting, bronchospasm, miosis (excessive pupil contraction), blurred vision, headache, cognitive impairment, seizure, and coma. An intermediate syndrome involving respiratory paralysis and failure may occur 1–5 days after exposure to some organophosphates. Irreversible weakness, ataxia (failure of muscle coordination), and paralysis may occur 2–5 weeks later. This delayed distal polyneuropathy is due to degeneration of myelin sheaths covering large nerve fibers.

Acute clinical organophosphate and carbamate poisoning is likely to appear when cholinesterase activity is inhibited by 50% or more, and 30% inhibition has been proposed by WHO as a hazard level. In studies of organophosphate pesticide exposure among U.S. workers, 20–40% of

1939: Insecticidal potential of DDT discovered in Switzerland, leading to synthesis of thousands of chemicals. Chlorinated hydrocarbons such as DDT, BHC, dieldrin, aldrin, chlordane, toxaphene, and others, all powerful contact and stomach poisons, see enthusiastic use against malaria and other insectborne diseases



1940s: Herbicides of the phenoxyacid group, notably 2,4-D, gain widespread use for controlling broadleaf weeds in corn, sorghum, small grains, and grass pastures

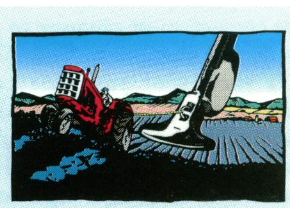
1950s: Fungicides captan and glyodin appear; organophosphorous insecticide malathion is introduced

1950s: By mid-1950s, synthethic organic compounds account for 90% of all pesticides used in U.S. agriculture

1961: DDT registered for use on 34 different crops as pesticide usage dramatically increases

1962: Rachel Carson publishes *Silent Spring*, an environmentalist's rallying cry against pesticide use

1970-80s: Herbicidal sulfonylureas, synthetic fungicides metaxyl and triadimefron, and light-stable pyrethroid pesticides introduced



1990s: Renewed interest in integrated pest management; intensified research on biological pest control methods and other alternatives to pesticides farm applicators show small, but statistically significant, reductions in plasma cholinesterase levels, some with symptoms of toxicity. Even higher percentages are reported in migrant farm workers, factory workers, and formulators. Cumulative cholinesterase inhibition can occur after exposures that do not produce clinical signs or symptoms. Thus, additional exposure in someone with already depressed levels of cholinesterase due to chronic exposure is more likely to cause a toxic effect .

Peripheral neuritis, which lasts 12–18 hours, has been associated with chlorophenoxy herbicides and pyrethroid insecticides. Organomercury fungicides and organochlorine insecticides may cause chronic neurotoxic effects linked to lesions of the central nervous system.

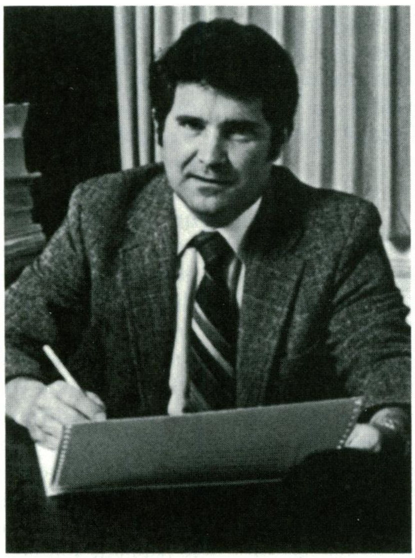
In Hopewell, Virginia, in 1975, the organochlorine insecticide chlordecone was responsible for more than 57 cases of neurological disease when industrial hygiene practices were not followed. Several exposed workers continued to show signs of illness four years after exposure. In July 1985, severe illness occurred in more than 1300 people in the western United States just a few hours after they had eaten watermelons treated with aldicarb, a nonregistered (illegal) use of the carbamate insecticide. Symptoms included nausea, vomiting, diarrhea, involuntary muscle contraction, mood changes, and other symptoms of cholinergic toxicity.

Skin Disorders. Agricultural chemicals have long been associated with skin disorders, especially dermatitis. During pesticide contact, most exposure to pesticides is via dermal absorption. Skin effects typical of a variety of pesticide compounds include contact dermatitis, skin sensitizaion, allergic reaction, rash, photoallergic reactions, and chloracne. Hexachlorbenzene, which is no longer registered for agricultural use, causes acquired toxic porphyria, severe cutanous reactions including deep scarring, permanent loss of hair, and skin atrophy.

Pulmonary Effects. The contact herbicide paraquat is a quaternary ammonium compound that can cause severe and progressive lung damage resulting in anoxia and death. However, most instances of human toxicity due to paraquat have resulted from suicide attempts. Acute renal failure and liver dysfunction also may be seen in paraquat poisoning. In addition, the bronchospastic effects of orgonophospates and carbamates can exacerbate asthma attacks.

Chronic Health Effects

Of growing concern are a number of chronic health effects from pesticides that do not occur immediately after exposure. Among these are carcinogenic, neurologic, reproductive, pulmonary, immunologic, and developmental effects. "The lengthy interval between exposure and chronic effects makes risk assessment for these outcomes more difficult to evaluate than acute effects," Blair points out.



B. Branson

Aaron Blair — No chemical class of pesticides can be considered problem free.

Establishment of a formal testing program by NCI in 1968 was continued by the National Toxicology Program (NTP) in 1978. This gave an early start to carcinogenic screening of pesticides and also stimulated epidemiologic investigation of pesticides and cancer. The availability of cancer registries also provided a source of information on well-diagnosed cases.

The issue of whether currently available data are sufficient for estimates of a pesticide-related cancer rate for the general population is not much debated today. What is debated is what the exact risks are. Richard Schmidt, Deputy Director of EPA's Health Effects Division, agrees with those who say the rate [of cancer] must be small when compared with other factors such as smoking. According to Schmidt, the public perceives a greater risk from pesticides than the scientific community. This point has been made even stronger by others. In his 26 February 1993 editorial in *Science*, Philip H. Abelson notes that other factors may be far more significant risks than consuming pesticide residues, saying, "The regulatory level [for pesticide exposure] is then set with the objective that individuals consuming the food for 70 years would have, as an upper limit, one extra chance in a million of incurring cancer. In contrast, the probability of suffering a cancer-caused death from a bad diet (e.g., excessive fat) is about 70,000 chances in a million." Based on data such as these, Abelson reaches the opinion that, "Synthetic pesticides in marketed foods constitute no appreciable threat to human health."

Cancer. NCI's Blair is not so sure. In regard to cancer alone, he notes that NCI-NTP bioassay findings of carcinogenicity are not restricted to a few chemical classes. "No chemical class of pesticides can be considered problem free," said Blair. Carcinogenicity has been associated with insecticides (organochlorines, organophosphates, carbamates, and pyrethrins), herbicides, and fungicides. "At least 45% of chemicals tested had an effect on at least one sex of one rodent species in these bioassays," Blair states.

Further indications for human risk come from epidemiologic observations of excess types of cancer in occupational groups with significant pesticide exposures. In more than two-thirds of farmers, excesses for Hodgkin's disease, multiple myeloma, melanoma, and cancers of the lip, skin, prostate, connective tissue, and brain occur. More than half of the studies show excesses for non-Hodgkin's lymphoma, leukemia, and stomach cancer. These findings are derived from broad occupational surveys of morbidity and mortality. They have also been observed in case–controlled or cohort studies specifically designed to evaluate cancer risks.

Although risks for most excess cancers in agriculture workers are low (in the range of 1.5–3-fold), many studies, according to Blair, are likely to underestimate the true risk because of errors of omission on the part of subjects who were asked to volunteer names of the pesticide they used, rather than having to respond to a specific list. Says Blair, "This suggests many users might have been misclassified as nonusers."

Among farmers, data are strongest linking specific pesticide exposures to non-Hodgkin's lymphoma, leukemia, and multiple myeloma. Excess cases of lip and skin cancer are thought to be due to sunlight exposure. Recent studies have strengthened a weak link between soft tissue sarcoma and exposure to the phenoxyacetic acid and chlorophenol pesticides.

Organophospates and organochloride insecticides are associated with risk for non-Hodgkin's lymphoma. In addition, case–control studies have shown a significant increased risk of this cancer among farmers using the phenoxyacetic acid herbicide 2,4-D, with risks increasing threefold to sevenfold among those reporting use for 21 or more days per year. Organophosphate insecticides resulted in a significant 2.4-fold increased risk for non-Hodgkin's lymphoma, independent of 2,4-D, the risk being over threefold with

21 or more days of use per year.

Organochlorines, including DDT, have been associated with leukemia. Recently, herbicide use has been linked to prostate cancer. However, relatively few investigations have attempted to assess the cancer risk of exposure to any specific pesticides.

Underlying explanations for a pesticide exposure–cancer connection remain speculative. One hypothesis posits a role for organophospate pesticides through their inhibition of serine esterases which are critical to T-cell lymphocytes and natural killer cells. "This is interesting," explains Blair, "because immunodeficient persons have elevated risks for the same tumors found in excess among agricultural populations."

In regard to an oncogenic role for phenoxyacetic herbicides, mutagenesis tests and animal studies offer only weak support for the role of 2,4-D as a carcinogen. However, the pesticide has been shown to have other properties, which may lead to a selective growth advantage for cells already harboring a mutation thereby increasing cancer risk.

NCI researchers believe laboratory and epidemiologic findings may suggest broader public health implications. Several of the malignancies (multiple myeloma, non-Hodgkin's lymphoma, melanoma, prostate, and brain) appear to be on the rise in the general population of several countries around the world. Excesses of cancer of the brain, lymphatic, and hematopoietic systems have been observed in rural farm populations, which raise the possibility of nonoccupational exposure. However, farm families and hired workers perform many tasks that may result in exposures to potential carcinogens in addition to pesticides: diesel fuel and exhausts, organic solvents, gasoline, metal fumes, paints, zoonotic viruses, microbes, and fungi. Many members of the general population have contact with these same substances as well. Says Blair, "Explanations for cancer excesses observed among farmers may have important implications for cancer prevention in nonagricultural populations."

Neurotoxicity. Increasingly apparent from studies of acute and occupational exposure to a variety of pesticides is mild to severe deterioration in neurologic function. In a recent review of the literature, Dennis Weisenburger of the University of Nebraska Medical Center says chronic neurologic effects, which may be irreversible, are associated with exposures to organophosphate, organochlorine, and carbamate insecticides, as well as a variety of fungicides and fumigants. He points to one case–control epidemiologic study in which investigators found convincing evi-

IPM: An Old Approach Made New Again

Recognition of the real and potential health risks from pesticides, as well as the growing resistance of pests to chemicals, has led not only environmentalists, but farmers as well to look for alternatives to traditional pesticide use. One of the most rapidly advancing alternatives to conventional pesticide use in agriculture is integrated pest management (IPM). Despite recent publicity surrounding IPM as a new pesticide alternative, the concept has seen application in U.S. agriculture for more than 20 years.

According to the Environmental Protection Agency, IPM cannot be specifically defined as any one set of techniques. As an interactive, information-intensive process of managing pests that may involve numerous techniques, it is better defined by its ends instead of its means. Most frequently it has been characterized practically as preventing pest outbreaks, economically as maximizing profits, and environmentally as minimizing pesticide use.

"IPM's main goal is not to get rid of chemicals, but to use them more judiciously to prevent resistance and destruction of beneficial insects."

IPM is a holistic approach to agriculture that may employ techniques including careful monitoring of pest populations, exploitation of natural predators and processes, judicious use of selective pesticides, artificial disruption of pest populations, and mechanical methods of pest control such as soil aeration, crop rotation, tillage or no-till, tractor-mounted flaming devices, vacuuming machines, and use of pest barriers.

"IPM is basically a very site-specific, information-intensive concept," says Anne Leslie, a chemist in EPA's IPM section. "It depends on the system you want to manage. We emphasize control of the pest rather than the crop. Pesticides are only one tool among many. This is not a case of managing pesticides."

According to Ronald Kuhr, professor of entomology and toxicology at North Carolina State University, a powerful incentive to IPM implementation is pesticide resistance. Currently, 504 of the most serious pest insects and mites show documented resistance to one or more classes of chemical controls. "IPM's main goal is not to get rid of chemicals," Kuhr says, "but to use them more judiciously to prevent resistance and destruction of beneficial insects."

Drawbacks to IPM include cost and complexity. A savings in pesticide costs through reduced use might be lost when opting instead for more expensive biological products and other natural methods. For example, a "trap crop" might be used where attractant pheromones specific to a pest are applied to lure the pest to a crop that hasn't been planted for harvest. Though no pesticide is used, acreage must be set aside, and the biological substance and its application must still be paid for. IPM may also require hiring field consultants to monitor the crop regularly, sometimes daily, to count pests as well as beneficial insect predators.

Another factor that adds to the complexity of IPM is that the program may need to be structured around the growing cycle, during which least-toxic, highly specific chemical pesticides and other pest control methods are applied according to an economic or "action" threshold, the level of insect on the crop that can be tolerated before a control measure is applied. Economics figure in here. This threshold is a point at which the damage caused by the pest equals the cost of a pest-control measure.

Says Kuhr: "If you're a farmer who's used to calendar spraying and seeing no insects on the crop, and then someone comes along and says you can lose 10–15 % of your crop to insects without hurting your yield, chances are you'd be reluctant at first." This reluctance, he adds, persists particularly among farmers of large acreage crops with small profit margins. However, where IPM has been proven effective and economical, it has rapidly won approval.

IPM has also won the approval of the Clinton administration, which included in its recent pesticide reduction plan the goal of 75% usage of IPM by the nation's farmers by the year 2000. Current use is estimated at 20%.

dence of chronic central nervous system deficits in workers with a history of a single clinically significant episode of acute organophosphate intoxication. These farm workers did poorer than controls on tests of auditory attention, visual memory, dexterity, motor steadiness, sequencing, and problem solving.

Only a few disparate epidemiologic investigations have associated Parkinson's disease and Parkinsonian symptoms with agricultural work and pesticide exposure. However, a recent well-designed, population-based case–control study in Canada suggests a dose–response relation between Parkinson's disease risk and cumulative lifetime exposure to field crop farming and to grain farming. Moreover, previous exposure to herbicides was consistently the only significant predictor of Parkinson's disease risk when potential confounding interactions were controlled.

Immune Effects. Immune effects of pesticides have been demonstrated in laboratory studies, but little evidence exists that pesticides can compromise human health through immune system interference. Further study may clarify any link. For example, common dermatitis due to pesticides is more common than previously thought. Impaired immune cell responsivity accompanied by increases in respiratory infections has been associated with length of organophosphate exposure. Pesticides can trigger asthma-type reactions. Altered immunoglobulin and complement levels and changes in T-cell populations have been noted after pesticide exposure. However, such immune system alterations may be short lived.

Anne Dowie

Jennifer Curtis—Federal monitoring and testing of pesticides is incomplete.

Reproductive Effects. Human reproductive effects of specific pesticides have been reported for the organochlorines, dibromolchloropropane and chlordecone (oligospermia and decreased sperm motilty). Wives of men exposed to dibromolchloropropane showed an increase in spontaneous abortion. Decreased sperm counts, motility, and viability along with sterility in males have been associated with ethylene dibromide exposure. Effects among males also include abnormal sperm morphology associated with exposure to the carbamate insecticide carbaryl.

Birth Defects. Reviews of the literature on reproductive effects of pesticide exposure point out that approximately 50% of active pesticide ingredients tested prove teratogenic in animals. To what extent they might contribute to birth defects in humans receiving much lower exposures remains unknown.

Some epidemiologic studies have suggested that pesticide use could be linked to a variety of congenital malformations in people in farm communities. These include facial clefts, limb reduction defects, cardiac, and urogenital defects. Chronic neurotoxicity, including cerebral palsy, has been reported as a result of perinatal pesticide exposure. Among female floriculture workers in Colombia who were occupationally exposed to pesticides, there was an increase in abortions, infant prematurity and congenital malformations. And among offspring of Vietnam veterans exposed to pesticides during the war, a study revealed increases in spina bifida, facial clefts, and neoplasms during the first year of life.

Neurotoxic effects of pesticides on the developing fetus were among the concerns of the 1993 National Research Council report, *Pesticides in the Diets of Infants and Children.* To those on the NRC committee, sufficient data strongly suggested that prenatal pesticide exposure to neurotoxic compounds at levels considered safe for adults could result in permanent loss of brain function if exposure occurred during the period of brain development.

NIEHS Senior Science Advisor James Fouts says a major concern is delayed, low-level effects of pesticide exposure, especially to susceptible populations such as pregnant women, the fetus, and newborns. "These are delayed effects, chronic, low-level, or subtle, effects. What we have with pesticides is a black hole. We don't have much of a research base to make predictions." Needed, he says, is more research in young animals, *in utero* and postnatal. Prospective studies beginning with migrant workers as a starting point are also needed, Fouts says.

Jennifer Curtis, National Resources Defense Council scientist, says concerns among scientists and the public about adverse health effects from pesticide exposure are well founded. "FDA monitoring of foods looks at only half the chemicals currently used in agriculture. And many older pesticides still in use on foods have not been adequately tested by EPA," she says.

Uncertainties in Risk Assessment

Today, two statutes govern regulation of pesticides: FIFRA, which authorizes the registration of individual pesticide products, and the federal Food, Drug, and Cosmetic Act, the major U.S. food safety law, which authorizes the setting of tolerances for pesticide residues in foods.

Tolerances are the level of chemical residue in or on a food above which adverse health effects are possible. EPA sets tolerances based on the amount of pesticide residue that remains in or on a crop after it is treated with the pesticide at the proposed maximum allowable rate. For almost all chemically related toxic effects, such as birth defects, reproductive, or noncarcinogenic chronic effects, EPA considers the results of toxicology studies of the pesticide's effects on animals; data on potential human exposure to residues in the consumption of foods; and an estimation based on these data comparing estimated potential dietary exposures to a calculated "acceptable" level for human intake. EPA then decides if it will set a tolerance for a particular pesticide and food combination.

When animal studies indicate that a pesticide chemical has induced cancer at relatively high dose levels, EPA ordinarily presumes there is no dose at which some level of carcinogenic effect would not be observed. As an index for regulatory decisions regarding carcinogens, EPA's policy is that lifetime incremental cancer risks from exposure to a pesticide in the diet should not exceed 1 in 1 million, meaning 1 in 1 million risk over and above the background cancer risk. This is the concept of "negligible" risk applied by EPA and FDA.

In 1993, an NRC committee examined current methods used in characterizing risk to infants and children from pesticide residue in foods.[See "Kids at Risk," Forum, *EHP* 101(5)]. Pediatrician Philip J. Landrigan of Mt. Sinai School of Medicine in New York chaired the committee. He points out that most animal testing on pesticide exposure uses mature animals. "Of particular importance are tests for toxicity to the developing immune, nervous and reproductive systems," he says. And according to the NRC report, there is no simple way to predict which compounds will represent greater hazards for infants or children or adults.

NRC committee Co-chair Donald R. Mattison, of the Graduate School of Public Health, University of Pittsburgh, says the biology of experimental animals, while generally similar to humans, can differ in critically important ways for toxicology. "These differences are of special concern for developmental toxicology," says Mattison. "If toxicity occurs, will it impair the potential for growth and development and result in long-term adverse health consequences?" In general, uncertainties in this step are entailed in making extrapolations to humans from high-dose animal studies or from comparing expected levels of reponse in humans to background occurrence rates and response in animals over and above those of laboratory control groups.

NRC committee members also took issue with the no-observable-effect level (NOEL) for noncancer effects, or reference dose, used by EPA to calculate acceptable human pesticide exposure from food. The reference dose is the level of exposure that EPA judges an individual could be exposed to on a daily basis for a lifetime with minimal probability of experiencing adverse effects. This is typically expressed in terms of milligrams of pesticide per kilogram of body weight per day.

"Unfortunately, we do not know with certainty what the precise exposure is, not for the average American and not for subpopulations of Americans such as infants and children," said James N. Seiber, NRC committee member and University of Nevada environmental toxicologist, in a hearing before a congressional committee on agriculture. While these uncertainties, he points out, have led to to the use of safety factors in regulating residue intakes, "the margin of safety provided by these factors may vary for population subgroups, such as infants and children." The NRC report, however, recommends that EPA employ a stricter standard when there's evidence of early childhood toxicity, "or when data from toxicity testing relative to children are incomplete."

NRC committee members concluded that much of the random government surveys of pesticide residues are conducted on the raw agricultural commodity, rather than on food as consumed. They noted a lack of data on how prepared food might alter, or reduce, food residues. Moreover, says Seiber, "many of the foods most consumed by children are not sampled frequently enough by FDA and the states to get a comprehensive picture of what levels [of pesticides] . . . are in kids' diets." Seiber says there is much data on residue intake from water used in preparing food items, which could add to the total residue intake.

Says Mattison, "Infants and children frequently consume a smaller number of foods, plus they consume greater quantities of food on a body-weight basis. Children frequently ingest single food items in amounts which are many times greater than adults. Indeed, the committee found differences in consumption of single food items to be the most significant difference with respect to potential pesticide exposure in foods between infants, children, and adults."

Curtis raises another issue of uncertainty concerning exposure analysis. She faults EPA for not paying attention to the cumulative effect of multiple chemicals in different classes of compounds when setting food tolerances. "Not only might pesticide residues be present on more than one food, multiple pesticide residues may be present on one food sample. This can be resolved by setting a tolerance for a food type."

Then there are risk assessment uncertainties associated with procedure differences among analytic laboratories, where analyses of the 600 or so pesticides and their breakdown products differ, and there are differences in methods of reporting data. Data gaps can also be key sources of uncertainty. Gaps may exist because of specific measurements or because studies that would complete an assessment are missing. Or a data gap may be broader, revealing an underlying lack of understanding about how a chemical interacts with the cells of the body to produce an adverse health effect.

In terms of data gaps regarding pesticides in the diets of infants and children, according to the NRC, there are no data taking into account developmental changes during infancy and childhood, different susceptibilies between children and adults, the fact that children are exposed to multiple pesticides in a single food item, or are exposed to the same pesticide or pesticides that act by the same mechanism on different foods and by different routes. The latter two sources of uncertainty in assessing dietary pesticide risk apply not only to infants and children, but to adults also.

On 25 June 1993, the Clinton administration announced its commitment to reduce the use of pesticides and to promote sustainable agriculture. Five days later the National Academy of Sciences released its long-awaited NRC report on pesticides in the diets of infants and children stating that children may be at far greater risk from pesticides than adults. On September 21 a plan was released by the Clinton administration for the EPA to reassess all pesticides used on fruits and vegetables in the United States and reduce the use of certain high-risk pesticides by the year 2000. The plan would implement a new standard to replace the current and often conflicting food safety laws, including the Delaney Clause of the Food, Drug, and Cosmetic Act which allowed no carcinogenic pesticide residues on food, with a uniform standard requiring that pesticides pose "a reasonable certainty of no harm." The plan also calls for the use of innovative pest management techniques by 75% of farmers by the same deadline, in which crops are sprayed only when pests are detected rather than on a fixed schedule.

Nowhere in the administration's announcement, the NRC report, nor among any of the critics, has there been any call for an abrupt termination of pesticide use. There is, however, a shared view that it will be possible in the long run to considerably reduce the use of traditional pesticides through alternative farming methods such as integrated pest management, use of biotechnology products, and organic farming methods. Thus, the administration's commitment to pesticide use reduction appears to be a dramatic shift in policy in light of the fact that funding for sustainable agriculture research currently makes up less than 1% of USDA's overall agricultural research budget.

Already, several pieces of legislation on pesticide policy issues have been proposed that may require the 103rd Congress to confront divided and deeply held positions by various interest groups including critics of pesticide regulatory practices, agribusiness, and food and chemical industries. The challenge on all sides will be to confront the scientific and other data gaps so that effective legislative decisions may be made that take into account both the economic benefits of pesticides as well as their potential and real dangers to public health.

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